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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/580,523	05/30/2000	Xiao-Mai Zhou	A7483	8284

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/580,523	ZHOU, XIAO-MAI	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,10,13,16,19,22,25 and 31-61* is/are pending in the application.

4a) Of the above claim(s) *31-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,10,13,16,19,22 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 2, 28.

Accordingly, claims 1, 3, 10, 13, 16, 19, 22, 25 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARGRAPH, SCOPE, NEW REJECTION

Claims 1, 3, 10, 13, 16, 19, 22, 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant BAD, having the amino acid sequence of SEQ ID NO:1, wherein the amino acid serine at position 118 is replaced with alanine or a conservative amino acid of alanine, wherein said mutant BAD has cell death promoting activity in vitro, **does not reasonably provide enablement for** 1) a mutant BAD which has an amino acid sequence "**95% homologous to SEQ ID NO:1**", and which has an amino acid substitution at the position "**corresponding**" to position 118 of SEQ ID NO:1, wherein said amino acid is alanine or an amino acid conservative for alanine, wherein said mutant BAD has cell death promoting activity in vitro, 2) a fragment of said mutant BAD, and wherein **said fragment has "cell death promoting activity" in vitro**, or 3) a mutant BAD or a fragment thereof, wherein said mutant or fragment thereof binds Bcl-XL or Bcl-2, or both, through a domain that is at least **"75% homologous**" to a BH3 domain of a "**naturally-occurring**" or wild type **mammalian BAD** or 4) A mutant BAD or fragment

thereof **"comprising" an amino acid sequence "corresponding" to position 103-123 of SEQ ID NO:1**, with the proviso that the amino acid at the position **"corresponding"** to position 118 or SEQ ID NO:1 is alanine, or an amino acid conservative of alanine, wherein said mutant BAD or fragment thereof has cell death promoting activity in vitro. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 3, 10, 13, 16, 19, 22, 25 are drawn to:

1) a mutant BAD which has an amino acid sequence **"95% homologous to SEQ ID NO:1"**, which has an amino acid substitution at the position **"corresponding"** to position 118 of SEQ ID NO:1, wherein said amino acid is alanine or an amino acid conservative for alanine, wherein said mutant BAD has cell death promoting activity in vitro (claims 1, 3, 10, 16, 19, 22),

2) a fragment of said mutant BAD, wherein **said fragment has "cell death promoting activity" in vitro** (claims 1, 3, 10, 16, 19, 22),

3) a mutant BAD or a fragment thereof, wherein said mutant or fragment thereof binds Bcl-XL or Bcl-2, or both, through a domain that is at least **"75% homologous"** to a BH3 domain of a **"naturally-occurring"** or wild type **mammalian BAD** (claim 13), and

4) A mutant BAD or fragment thereof **"comprising" an amino acid sequence "corresponding" to position 103-123 of SEQ ID NO:1**, with the proviso that the amino acid at the position **"corresponding"** to position 118 or SEQ ID NO:1 is alanine,

or an amino acid conservative of alanine, wherein said mutant BAD or fragment thereof has cell death promoting activity in vitro (claim 25).

The specification discloses a mutation of murine BAD of SEQ ID NO:2, wherein the serine at position 155 is replaced by Alanine, abolishes the phosphorylation of the murine BAD, and heterodimer formation with Bcl-X_L , and wherein Serine 155 is located at the center of the BH3 domain, and phosphorylation of Serine 155 promotes cell survival (Examples 1-2, on pages 72-77, and Example 9 on pages 87-93). The specification also discloses that BAD is a death promoter polypeptide, when heterodimerization with Bcl-X_L, a survival promoter, suppresses the survival promoting activity of Bcl-X_L, and promotes cell death activity. The specification discloses that phosphorylation of BAD at Serine 112, or Serine 136 or Serine 155 of murine BAD of SEQ ID NO:2 would abolish the binding of BAD to Bcl-2 or Bcl-X_L , and thus abolish the death promoting activity of BAD (p.4, first paragraph and Examples 1-2, 9). The specificataion discloses that SEQ ID NO:1 is the human BAD, wherein the serine at position 118 correspond to the serine 155 of the murine BAD of SEQ ID NO:2 (p.7, and40-41, and table 1 on page 42). The specification further discloses mutants of BAD having a domain substantially similar to the BH3 domain, and an amino acid different from Serine at a position corresponding to position 118 of SEQ ID NO:1, as identified by alignment of the mutant sequences with SEQ ID NO:1 (p. 10-17). There is however no disclosure that these mutants have cell death promoting activity.

The specification further discloses that when Serine 155 of murine BAD is replaced with Aspartic acid (S155D), there is no pro-apoptotic activity of the S155D mutated BAD as compared to wild type BAD (p.89, second paragraph, and figure 12C).

It is noted that the Serine 155 of murine BAD is within the BH3 region of murine BAD, which comprises the amino acid positions 151 to 159 of murine BAD or SEQ ID NO:2 (specification, page 13, last paragraph). In addition, it is noted that it is well known in the art that the BH3 region of BAD is necessary for binding and forming heterodimer with Bcl-2 molecules, and that a conformational change possibly take place in either Bcl-2 or the BH3 peptide upon binding (Letai, A et al, 2002, Cancer Cell, 2: 183-192, especially page 188, first column).

It is further noted **since there is no definition of "corresponding", an amino acid position corresponding to position 118 could be an amino acid at any position, and an amino acid sequence "corresponding" to position 103-123 of SEQ ID NO:1 could be any amino acid fragment of any structure**.

In addition, it is noted that a naturally occurring mammalian BAD encompasses an allelic variant of any wild type mammalian BAD, or an allelic variant of SEQ ID NO:1.

Claims 1, 3, 10, 13, 16, 19, 22, 25 encompass:

1) **a variant, having unknown structure**, of the mutant of SEQ ID NO:1, wherein said mutant of SEQ ID NO:1 has an amino acid substitution at the position 118 of SEQ ID NO:1, or at any position of SEQ ID NO:1, wherein said amino acid is alanine or an amino acid conservative for alanine, wherein said mutant BAD has cell death promoting activity in vitro,

2) **a fragment of said mutant BAD of any length**, wherein said fragment has "cell death promoting activity" in vitro,

3) a mutant BAD or a fragment thereof, wherein said mutant or fragment thereof binds Bcl-XL or Bcl-2, or both, through a domain that is **a variant of** a BH3 domain of a **"an allelic variant"** of or wild type mammalian BAD (claim 13), and

4) A mutant BAD or a fragment thereof **comprising unknown sequences attached to any amino acid sequence fragment of any structure**, with the proviso that one amino acid at any position of said mutant or a fragment thereof is alanine, or an amino acid conservative of alanine, wherein said mutant BAD or fragment thereof has cell death promoting activity in vitro.

One cannot extrapolate the teaching of the specification to the scope of the claims. The scope of the claims includes numerous structural variants. Applicants have not shown how to make and use the claimed variants which are capable of functioning or have the properties of inducing cell death in vitro.

The claims read on variants of the serine118 to alanine118 mutant of SEQ ID NO:1, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural variants. The specification and the claims do not provide any guidance as to

which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated. No consensus sequence for the claimed polypeptides is disclosed in the specification.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the claimed polypeptide variants would have properties of promoting cell death. It is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are

exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The specification does not disclose how to make the claimed polypeptide variants, such that they would function or have the properties as claimed, or how to use said polypeptide variants if they did not have the function or properties claimed.

Concerning the claimed **fragments of said mutant BAD, wherein said fragment is of any length**, and wherein said fragment has "cell death promoting activity" in vitro, Applicant has not taught how to make said fragments, such that they would function as claimed. It is noted that although BH3 domain is necessary for binding and forming heterodimer with Bcl-2 molecule, it is unpredictable whether the BH3

domain alone is sufficient for promoting cell death activity, or which part(s) of SEQ ID NO:1, besides the BH3 domain, or the full length sequence comprising said BH3 domain having Alanine118 is required for promoting cell death activity, especially in view that heterodimerizing with Bcl-2, and a conformational change of either Bcl-2 or the BH3 peptide are required following binding of BH3 peptide, for the function of BAD molecule (Letai et al, 2002, of record). In view of said unpredictability, it would be undue experimentation for screening the claimed fragment of the mutant BAD, wherein said fragment promotes cell death.

Concerning the claimed mutant BAD or a fragment thereof, wherein said mutant or fragment thereof binds Bcl-XL or Bcl-2, or both, through a domain that is **a variant of** a BH3 domain of a **"an allelic variant"** of or wild type mammalian BAD, Applicant has not taught how to make a variant of BH3 domain such that it would function as claimed and consequently Applicant has not taught how to make said mutant BAD or a fragment thereof, such that it would function as claimed. The claims read on variants of the BH3 domain, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions. In view of the above unpredictability of protein chemistry, it would have been undue experimentation for one of skill in the art to make the claimed mutant BAD or a fragment thereof comprising a variant of BH3 domain, such that it would function as claimed.

Moreover, Applicant has not taught how to make the allelic variants of mammalian BAD including allelic variants of SEQ ID NO:1, wherein said allelic variants

could have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the BAD wild type polypeptide, or of SEQ ID NO:1, as well as insertions and deletions. In view of the above unpredictability of protein chemistry, it would have been undue experimentation for one of skill in the art to make the claimed allelic variants of mammalian BAD including allelic variants of SEQ ID NO:1.

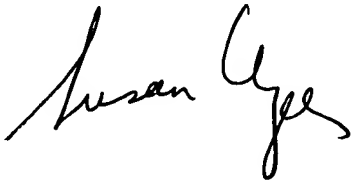
In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER



MINH TAM DAVIS

July 06, 2004